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Non-interventional study to investigate the efficacy and safety of Tegaderm™ Matrix in the treatment of patients with therapy-refractory chronic wounds

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- Tegaderm™ Matrix
- chronic wounds
- leg ulcers
- pressure ulcers
- diabetic foot ulcers

Summary

Background: Despite a variety of therapeutic approaches, many patients with chronic wounds remain refractory to treatment. Products such as Tegaderm™ Matrix were developed especially for such patients to alter the wound environment and reactivate the stagnant wound healing process.

Patients and Methods: In this prospective post-authorization observational product study, a total of 314 patients with therapy-refractory chronic wounds of various origins were evaluated. Beside to the wound area reduction and healing rate, the occurrence of adverse events was documented.

Results: On average the wounds were 10 months old. The average wound size was 17.3 cm^2 (median 6.3 cm^2) at the initial visit. In the course of treatment the wound size decreased to 13.0 cm^2 (median 3.5 cm^2) and was finally reduced to 9.3 cm^2 (median 0.9 cm^2) at end of the study. Taking the criteria of the European Wound Management Association for improving the quality of clinical studies into consideration, a wound size reduction of at least 50 % is the parameter for successful treatment of chronic wounds. This study demonstrated a wound size reduction of at least 50 % for 72.9 % of the patients with therapy-refractory chronic wounds when treated with Tegaderm™ Matrix. The safety profile was evaluated; only 4.7 % of the patients experienced a treatment-related adverse event such as a burning sensation.

Conclusions: The results of the study demonstrate that Tegaderm™ Matrix along with treatment of underlying causes is a well tolerated wound dressing promoting wound size reduction up to healing for the majority of patients with previously therapy-refractory chronic wounds.

Introduction

The treatment of therapy-refractory chronic wounds is an interdisciplinary challenge in daily routine practice. As the pathophysiologically relevant factors behind disturbed wound healing can be quite variable, a differential diagnostic classification of the causes for disturbed wound healing should be accomplished before initiating specific therapy [1, 2]. Even with therapy targeted at possible causes, wounds will not heal in a certain proportion of the patients. One reason may be the increasing number of factors in the wound environment reported in recent years that lead to a disturbed wound healing cascade. The focus has shifted here to the balance between matrix metalloproteinases (MMP) and their physiologic antagonists, the tissue inhibitors of metalloproteinases (TIMP) [3–6]. Therapeutic wound products that actively intervene in this process are therefore also termed active wound dressings or wound starters. One of these new active wound dressings is Tegaderm™ Matrix.

After several in vitro and initial clinical studies have demonstrated the efficacy of Tegaderm™ Matrix, the goal of our study was to examine the promotion of wound healing and the tolerability of Tegaderm™ Matrix on a larger patient population with previously therapy-refractory wounds under the realistic conditions of clinical practice.

Patients and methods

Patients

All patients with chronic wounds existing for at least 2 months demonstrating delayed wound healing despite adequate wound therapy could be included. Further, therapy of the underlying cause(s) should have been initiated, if possible, and continued unaltered within the framework of the study. Exclusion criteria were the presence of necrosis, clinically infected wounds and known contact

Table 1: Quantitative wound size analysis of the total patient population. *The last visit corresponds to the last observation carried forward method.

Wound size (cm^2)	Patients	Mean	Median
Initial visit	314	17.3	6.3
Follow-up visit	305	13.0	3.5
Final visit	304	9.3	0.9
Last visit*	314	9.3	0.9

sensitizations against components of the wound dressings employed.

Product and practical use

Tegaderm™ Matrix is a sterile wound dressing impregnated with an ointment consisting of polyhydrated ionogens (PHI). PHI contains in addition to citrate buffer a synthetic mixture of trace elements such as calcium, potassium, rubidium and zinc on a cellulose acetate carrier. Warmth and humidity allow for polyethylene glycol to release the formulation in the wound bed.

Tegaderm™ Matrix was applied to the previously cleansed wounds as a primary dressing. The secondary dressing was selected by the treating physician on the basis of the amount of wound exudate expected. The combined use with an alginate or hydrocolloid dressing was discouraged. Dressing changes were performed daily in the first 2 weeks and then every 2–3 days.

Observation period and temporal course

This non-interventional study had a prospective and non-controlled design as a post-marketing observational study. It started on February 2009 and ended in May 2010. The results of the physician examination were documented at 3 different points in time. The appointments for the physician-patient contacts were made on an individual basis; the time points of documentation were set, however. The individual observation period was 12 weeks at a maximum. Among others, wound size, wound base and surroundings were documented.

Participating centers

The study was performed by 93 physicians from the specialties dermatology (50.5 %), surgery (24.7 %) and general practitioners (20.4 %) in the entire Federal Republic of Germany.

Statistical analysis

The documentation sheets were forwarded for statistical analysis to the Institute Dr. Schauerte (Oberhaching, Germany) and registered in a data bank. Before the statistical analysis. a validation and analysis plan was developed. Coding of all documented diseases and unwanted events was performed according to MedDRA (version 13.1). The calculation of wound sizes from the size measurement of the treating physician was done according to the stipulation of Goldman and Salcido [7]. Statistical analysis included all observation criteria and was performed following descriptive and explorative statistical methods. These included beyond statement of total number and number of missing values – depending on scale level – statements on mean, median, largest and smallest value or frequency. Analysis was performed using the statistics program package SAS (version 0.2, SAS Institute Inc., Cary, NC, USA).

Results

Total patient population

A total of 364 patients were included in the study. These included 275 patients with leg ulcers (75.5 %), 29 patients with diabetic foot syndrome (8.0 %), 13 with pressure ulcers (3.6 %) and 47 patients with other types of wounds, radiation dermatitis, postoperative or post-traumatic wounds (12.9 %). On average the wounds had existed for 10 months. Of the patients 166 (45.6 %) were men and 198 (54.4 %) women with a mean age of 68 ± 15 years. The mean treatment duration with Tegaderm™ Matrix was 9.4 weeks within the context of the clinical study.

For the study of efficacy of Tegaderm™ Matrix exclusively, those data sets with wound size measurements being completely registered for all visits with at least 3 weeks of treatment with Tegaderm™ Matrix were taken into consideration. Overall 314 data sets fulfilled these criteria and were finally used in the calculation of the healing rate. The mean wound size at the initial visit was 17.3 cm^2 (median 6.3 cm^2). At the follow-up visit wound surface area was reduced to 13.0 cm^2 (median 3.5 cm^2) and was further reduced to 9.3 cm^2 (median 0.9 cm^2) (Table 1, Figure 1). As to the healing rate this signifies that in 40.8 % of patients a wound size reduction between 75 and 100 % was achieved, and that 17.8 % of the patients had a healing rate between 50 and 75 %. In a total of 45 patients (14.3 %) the wound healed completely (Table 2). Therapy with Tegaderm™ Matrix was able to achieve an at least 50 % reduction of wound area size in 72.9 % of patients with chronic, previously therapy-refractory wounds. An evaluation of the wound bed and wound edges was also performed during treatment. In addition to a reduction of the fibrin coat and increase of granulation tissue and epithelization, improvement of the wound edges was documented. The appearance of macerated, reddish and/or edematous wound edges shifts distinctly in the direction of intact wound edges (Figure 2a–d).

Besides the efficacy profile, safety and tolerability were evaluated. The data of all 364 patients were considered for this. Overall, 86.5 % of patients completed treatment ass planned. An interruption of therapy occurred in 1.1 % of patients and premature discontinuation of therapy in 12.1 %. The most commonly named reason for discontinuation of therapy was an increase in wound pain (3.6 %), but also other reasons such as "loss to follow-up" or inpatient treatment in hospitals which were not related to the product. Unwanted events (UE) were documented in a total of 39 patients. For 17 patients a causal relationship with the use of Tegaderm™ Matrix was reported and for another 11 patients a possible relationship was suspected. In 8 patients a connection could be excluded; for 4 further patients no further information was given. The UEs were encoded according to MedDRA and classified in clusters. In 11 cases a burning sensation in the wound and in 10 further cases wound pain after application of the dressing were documented. Besides this main cluster, in 5 patients

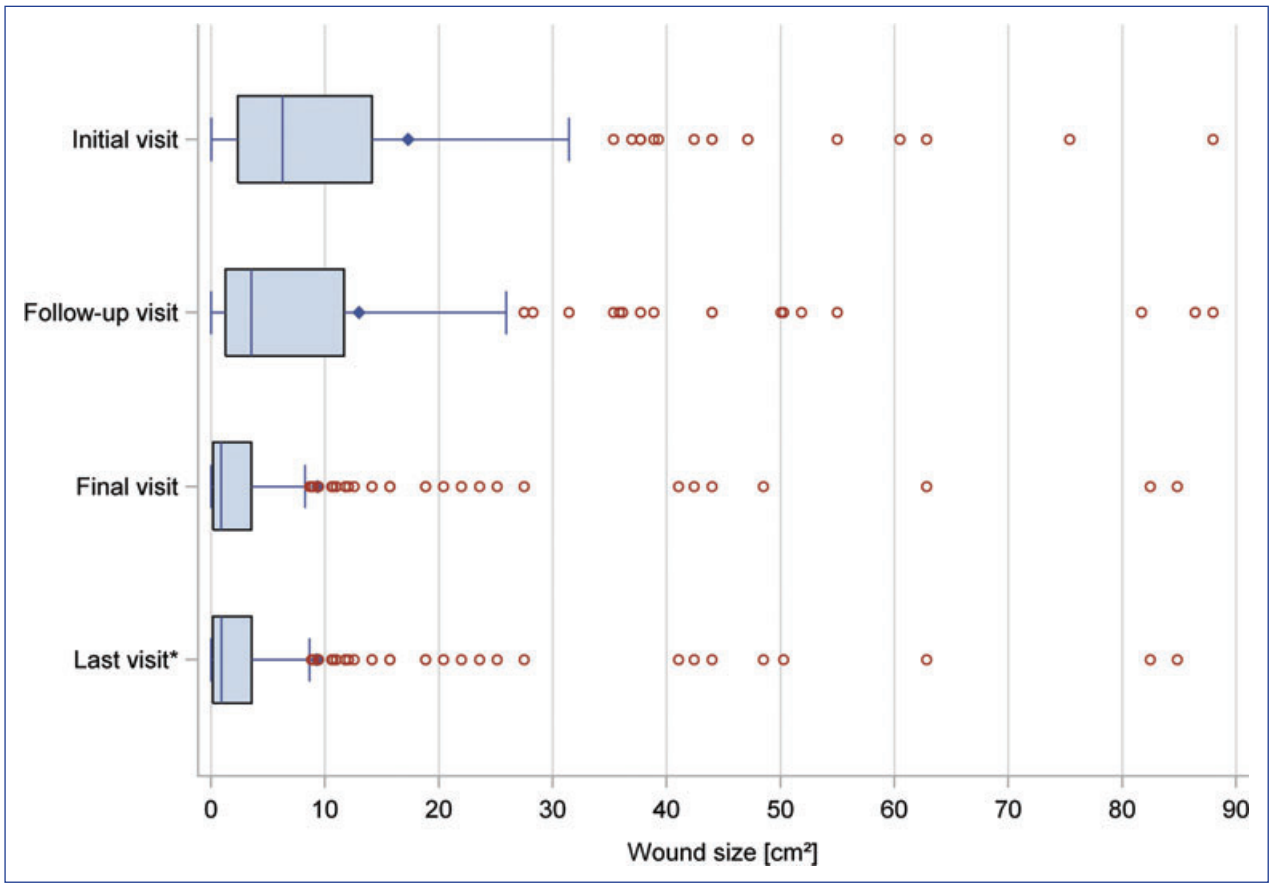

Figure 1: Wound size reduction based on the total patient population. To some extent very large wounds up to 475 cm^2 were included in the study. The boxplot shows only wounds with a maximum size of 90 cm^2 for better visualization of the effects. *The last visit corresponds to the last observation carried forward method.

Table 2: Wound size reduction of the total patient population. Data of patients with chronic wounds treated with Tegaderm™ Matrix for at least three weeks were evaluated.

Wound healing rate	Patients (absolute)	Patients (relative, %)	
Total	364	100	
Lack of statement on wound size	31	8.5	
Treatment < 3 weeks	19	5.2	
Data sets wound healing rate	314	100	
0 %	19	6.1	
0–25 %	27	8.6	
25–50 %	39	12.4	
50–75 %	56	17.8	**72.9%**
75–100 %	128	40.8	
100 %	45	14.3	

wound size increased, which was reported as an UE possibly connected with therapy. The remaining events are distributed to the clusters "alterations of the wound surface and immediate wound surroundings" (11 patients, 8 causal, 3 possibly causal), "initial wound infection" (2 patients, possibly causal) and one case of documented allergic contact dermatitis (1 patient, causal). In summary, 95.3 % of patients had no UE in causal connection with Tegaderm™ Matrix. The tolerability profile of Tegaderm™ Matrix can therefore be considered good.

The further description of the results will be made differentially according to the pathogenesis of the wounds by means of sub-group analyses.

Leg ulcers

The entity of leg ulcers represents the largest sub-group in this study. After examining the data sets for completeness the data sets of 231 patients were analyzed. Of these patients 135 were women (58.4 %) and 96 men (41.6 %). Mean patient age was 70 ± 13 years. With respect to etiology and pathogenesis, 173 patients had venous leg ulcers, 50 mixed leg ulcers (21.6 %) and 5 patients an arterial leg ulcer (2.2 %). In 3 patients (1.3 %) a statement on genesis was lacking. The duration of the wounds

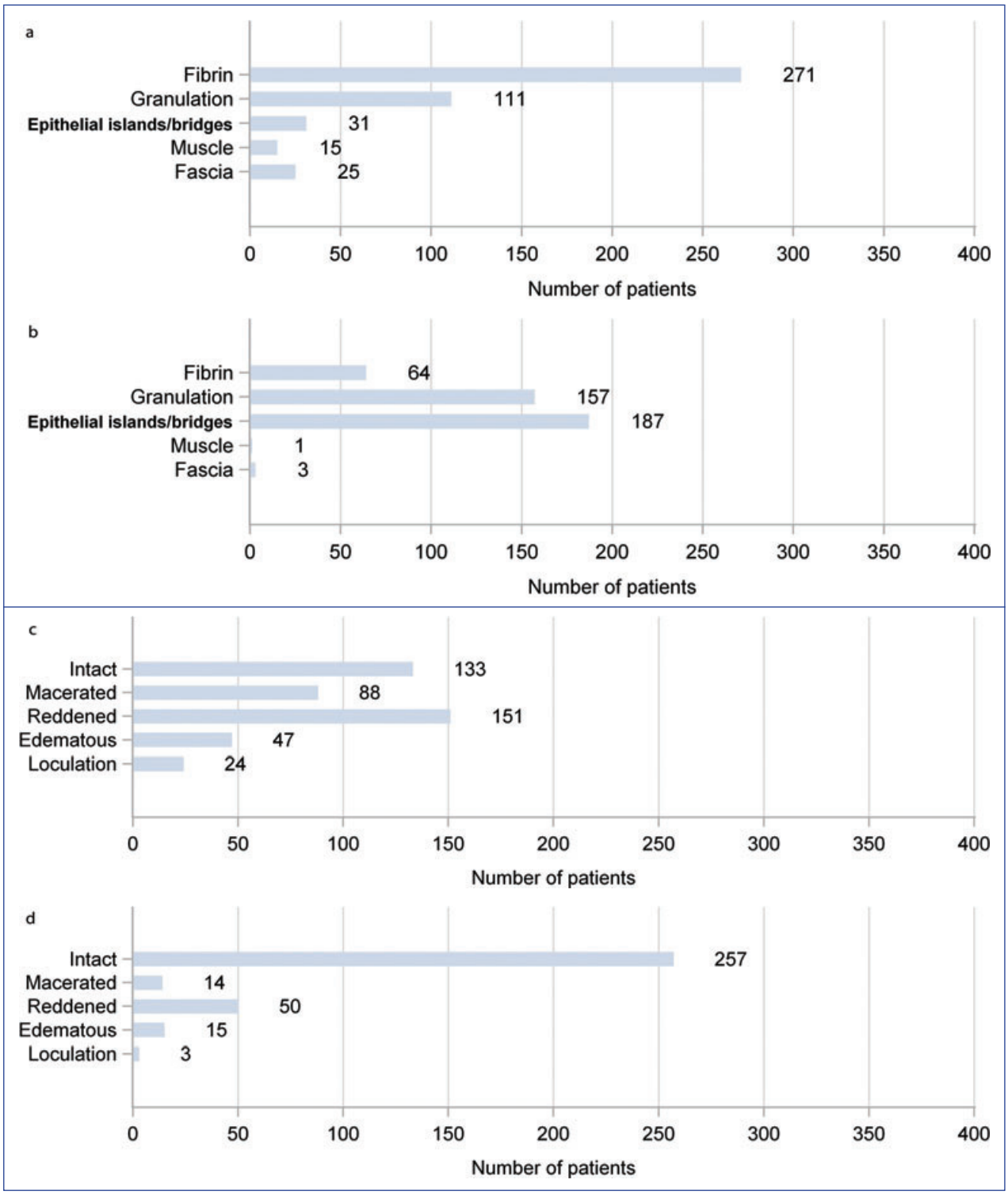

Figure 2: Wound bed (a and b) and wound edge (c and d) analysis based on the total patient population. Figures a and b show the initial diagnostic findings before therapy, b and d show the findings after the conclusion of therapy. Multiple answers were allowed.

ranged between 2 and 200 months, on average 12 months. A history of recurrent ulcers was reported by 104 (45 %) and pain by 176 (76.2 %) patients. On a visual analog scale (VAS) pain was rated as 4.3 points on average. Treatment duration with Tegaderm™ Matrix was 9.5 weeks on average. For calculating the healing rate those ulcers whose wound dimensions were recorded completely for all visits were analyzed. This was applicable to 207 data sets. At the initial visit the wounds were at least 0.1 cm^2 and maximally 475.2 cm^2 large. Mean wound size was 19.3 cm^2 (median 7.1 cm^2). The mean surface area at the follow-up visit was 14.6 cm^2 (median 4.7 cm^2) and at the final visit 11.7 cm^2 (median 1.6 cm^2) (Table 3, Figure 3). After completion of therapy 38.2 % of the patients demonstrated a reduction of wound size

Table 3: Quantitative wound size analysis of patients with leg ulcers. *The last visit corresponds to the last observation carried forward method.

Wound size [cm²]	Patients	Mean	Median
Initial visit	207	19.3	7.1
Follow-up visit	206	14.6	4.7
Final visit	204	11.7	1.6
Last visit*	207	11.8	1.6

between 75 % and 100 %, while 18.8 % of patients had a wound size reduction between 50 % and 75 %. On total 12.1 % of the wounds healed completely (Table 4). Taking the wound healing rates together 69.1 % of the patients achieved an at least 50 % reduction of wound size.

Pressure ulcers

Nine patients with pressure ulcers were analyzed, of these 6 women and 3 men aged between 64 and 89 years (on average 79 years). Wounds had existed on average for 8 months, being in the gluteal region in 6 patients, on the lower legs in 2 and on the back in one. The pressure ulcer was stage III in 7 patients and stage II according to Seiler in 2 patients. In 7 cases the wounds were recurrent. Of 6 patients pain was reported with a severity of 3.9 VAS points. Treatment duration with Tegaderm™ Matrix was on average 11 weeks. For determining the healing rate the data sets of 8 patients could be analyzed. Wound size at the initial visit was reported between 2.4 and 39.3 cm^2 with a mean size of 14.6 cm^2 (median 8.1 cm^2). At the follow-up visit mean wound size was 8.8 cm^2 (median 5.5 cm^2) and at the final visit 3.6 cm^2 (median 1.4 cm^2). An at least 50 % reduction of wound size was observed in 5 of 8 patients (62.5 %). One wound healed completely during the study time period.

Diabetic foot syndrome

Of the 22 patients with diabetic foot syndrome 17 were men (77.3 %) and 5 women (22.7 %). Age ranged between 41 and 83 years with a mean of 66 years. With respect to the stage according to Wagner stage I was reported in 7 patients (31.8 %), stage II in 9 patients (40.9 %), stage III in 4 patients (18.2 %) and stage IV in 2 patients (9.1 %). The wounds had existed for 2 to 60 months, on average for 11 months. According to history the ulcer was a recurrence in 8 patients (36.4 %); 9 complained of pain with a mean of 5.3 VAS points (40.9 %). Treatment duration with Tegaderm™ Matrix was 9.4 weeks on average. In the end the data sets of

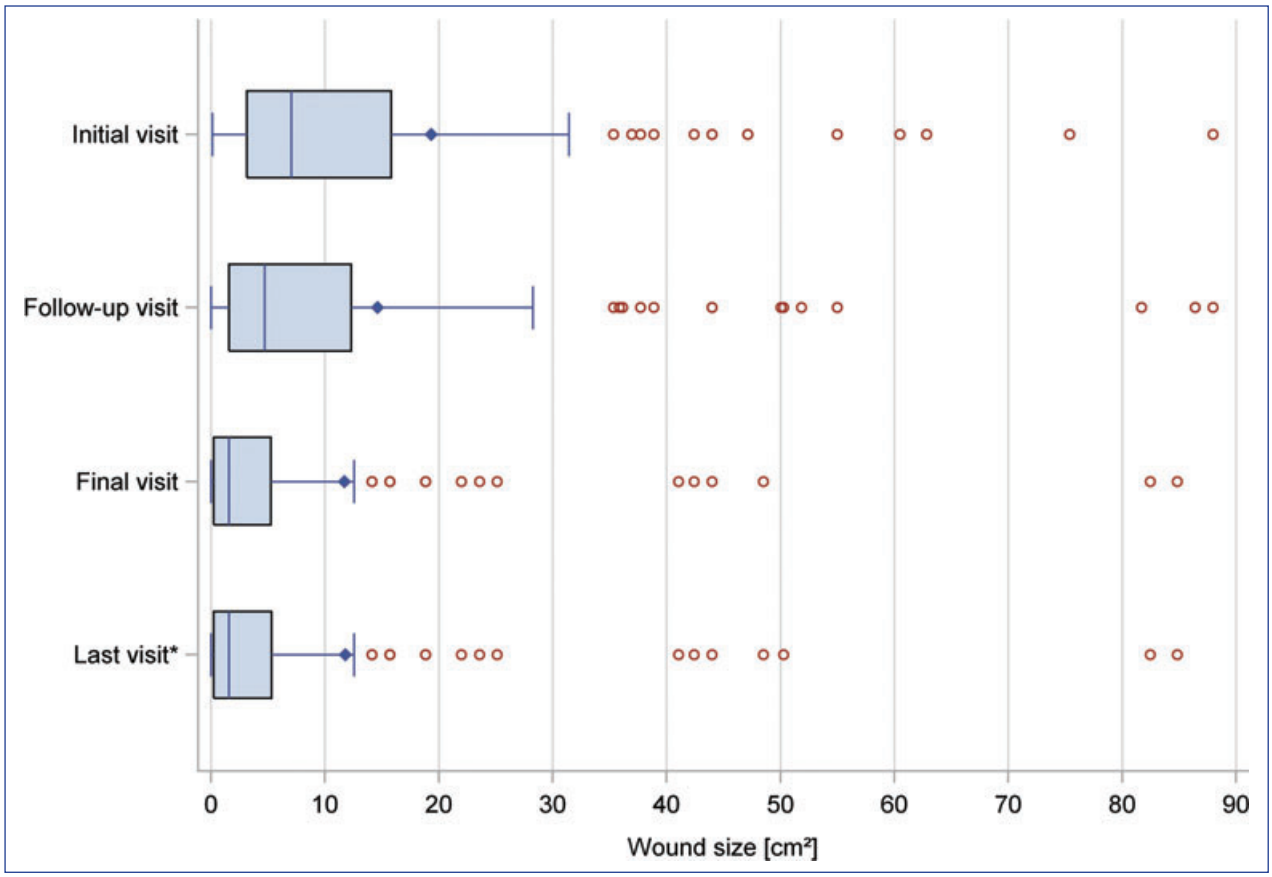

Figure 3: Wound size reduction in patients with leg ulcers. *The last visit corresponds to the last observation carried forward method.

Table 4: Wound size reduction in patients with leg ulcers.

Wound healing rate	Patients (absolute)	Patients (relative, %)
Total	231	100
Lack of statement on wound size	16	6.9
Treatment < 3 weeks	8	3.5
Data sets wound healing rate	207	100
0 %	14	6.8
0–25 %	22	10.6
25–50 %	28	13.5
50–75 %	39	18.8
75–100 %	79	38.2
100 %	25	12.1

69.1%

19 patients could be analyzed. The wound size at the initial visit ranged from 0.1 cm^2 to 23.6 cm^2 with a mean of 4.6 cm^2 (median 1.9 cm^2). At the follow-up visit the mean wound size had been reduced to 3.8 cm^2 (median 0.8 cm^2) and at the final visit to 2.8 cm^2 (median 0.5 cm^2). This corresponds to an at least 50 % wound size reduction in 63.2 % of the patients.

Discussion

Within the context of a complex treatment strategy of patients with chronic wounds targeted at the cause, the use of modern wound dressings is sensible, for example, to realize a moist wound environment with exudate management. It is suggested that in therapy-refractory cases selection of a wound dressing might potentially achieve renewed induction of stagnant wound healing [8]. Studies to date indicate that Tegaderm™ Matrix can have a positive effect on previously stagnant wound healing [9]. This is primarily attributed to a reduction of the pH value on the wound surface, which, among others, contributes to a reduced activity of the matrix metalloproteinases (MMPs) [9–11].

Clinical studies on Tegaderm ™Matrix

Several publications on the clinical use of Tegaderm™ Matrix or the identical product DerMax® are found in the current literature. Hamptom et al. demonstrated in a prospective case study the positive effect of Tegaderm™ Matrix in 23 patients with chronic, non-healing wounds. Overall, compete healing was achieved in 48 % of the patients [12]. Karim et al. describe the course of wound healing in 4 patients with chronic wounds during treatment with Tegaderm™ Matrix. Within the context of this study on day 0 and subsequently every 14 days a biopsy was taken from the center of the wound until the wound had healed completely. Histology revealed initially a high expression of MMP-2. After 14 days clinically a reduction of exudate was seen, but hardly any alteration in the immunohistochemical patterns. After 4 weeks in addition to a reduction of size, initial epithelization and further reduction of wound exudate are reported. Further there was now a reduction in MMP-2 expression that continued in week 6. The authors discuss that, among others, the reduction of MMP-2 expression readjusts disturbed wound healing and that the degree of MMP-2 expression during therapy with Tegaderm™ Matrix can serve as marker for beginning wound healing [13]. Lassance et al. were able to demonstrate in biopsies that during therapy with Tegaderm™ Matrix a normalization of previously elevated production of MMP takes place [14]. Also two further clinical studies on patients with chronic wounds showed good therapeutic success during treatment with Tegaderm™ Matrix. Pirayesh et al. treated a total of 20 patients with a therapy-refractory diabetic foot syndrome and a wound size over 2 cm^2 over 4 months. In 75 % of the patients total wound closure occurred within the observation period [15]. Van Leen et al. also treated 19 patients with pressure ulcers of stages II–IV according to Seiler over a maximum of 6 weeks. All patients with stages II and III healed completely. In the collective of patients with stage IV only 20 % healed [16]. In a prospective, open study by our working group a total of 5 patients with highly therapy-refractory chronic wounds were included. In addition to clinical wound assessment regular pH measurements of the wound surface and pain were recorded. All patients demonstrated a reduction of absolute wound size; in one patient complete healing of the wound occurred. Mean wound size was reduced from 13.5 cm^2 to 3.1 cm^2. Mean pain intensity sank from 1.4 before therapy to 0.62 during therapy and 0.4 at the end of the observation period. We were also capable of objectifying a previously not yet reported distinct fall in the pH value in the wound environment [9].

MMPs and wound healing

The exact interaction of MMPs – first reported in 1962 – in vivo has not yet been fully elucidated. A central responsibility of the group of MMPs is homeostasis of the extracellular matrix (ECM) and the basement membrane zone [17]. MMPs thus promote degradation of damaged cellular material, cell migration within the framework of re-epithelization and optimize tissue remodeling after wound closure [18]. Disturbed regulation of the interaction of MMPs and TIMPs results in increased damage to the ECM with subsequent tissue damage. Disturbed wound healing through a perpetuating inflammatory reaction is the consequence. Further, building blocks essential for undisturbed wound healing such as various growth factors can be degraded by MMPs. It has already been shown that in this complex interplay of various enzymes such as MMP-2, among others, due to increased degradation of collagen disturbed re-epithelization results [19, 20]. The content of MMP in exudate from chronic wounds is significantly increased in comparison to acute wounds [21, 22]. The first clinical studies were able to show that the use of modern wound dressings leads to a significant reduction of MMP-2 in wound exudate. This MMP-2 decline correlates directly with the wound size reduction or with the promotion of neoangiogenesis and re-epithelization [20, 23]. A modulation of the proinflammatory, catabolic wound

environment, for example by the use of Tegaderm™ Matrix, might represent a factor for the induction of wound healing particularly in therapy-refractory wounds.

PHI-5

The term PHI-5 denotes various metal ions in combination with citrate buffer as active ingredients of Tegaderm™ Matrix. During use of PHI-5 both a reduction of reactive oxygen species (ROS) as well as of MMP-2 could be demonstrated [11, 23]. Increased levels of these catabolic substances in the wound environment otherwise lead to forced degradation of growth factors and proteinase inhibitors. The resulting oxidative stress can further promote perpetuating inflammation and imbalance between tissue formation and degradation in chronic wounds [3]. In vivo studies prove that both a reduction of release of ROS from polymorphonuclear neutrophils (PMN) as well as an inhibition of complement activation can be achieved by PHI-5, so that the tissue-destroying cascade is interrupted and tissue protected [9]. In a study on guinea pigs it was shown that PHI-5 has positive effects on the healing of acute wounds. In this study with the exception of the control group increasing concentrations of PHI-5 were employed in the wounds. In the differential analysis a significantly reduced wound size was observed in the group treated with higher PHI-5 concentrations [24]. In none of the studies published to date was there any indication of cytotoxicity of the employed concentrations of PHI-5.

pH regulation

The activity of MMPs is directly dependent on the pH value of the environment. Optimum activity is assumed in the alkaline range between pH 7 and 8. In our own studies we found that in chronic wounds also usually an alkaline pH value around 7.4 exists [10]. In further studies it could then be demonstrated that by lowering the pH value by one log step a reduction of activity of various proteolytic enzymes in chronic wounds and in particular of MMP-2 by more than 80 % results [5]. As Tegaderm™ Matrix contains a citrate buffer and a lowering of the pH value on the wound surface has already been demonstrated [9], a wound healing-promoting effect by way of reduction or normalization of MMP activity and increased oxygen uptake can be discussed.

Own data

The "Patient Outcome Group" of the European Wound Management Association (EWMA) in a consensus declaration in 2010 defined a 50 % reduction of wound size as a parameter for successful treatment in clinical studies on patients with chronic wounds [25]. For this reason we placed particular emphasis on this value as a relevant aspect in clinical practice.

In the total group of 364 patients included in the study the course of wound size could be completely documented and analyzed in 314 patients. In 72.9 % of these patients with previously therapy-refractory wounds a reduction of wound size by at least 50 % could be achieved with Tegaderm™ Matrix. A total of 14.3 % of the documented wounds healed completely.

For the three most common entities of chronic wounds – leg ulcers, diabetic foot syndrome and pressure ulcers – subgroup analyses were performed. Of the 231 patients with leg ulcers complete documentation of wound size within the context of wound treatment was present for 207 patients and could be utilized for calculation of the healing rate. In 69.1 % of these patients treatment resulted in a wound size reduction of at least 50 %. Overall, 12.1 % of the patients exhibited complete healing. Of the 9 patients with pressure ulcers complete documentation of wound size was available for all three visits in 8 patients. An at least 50 % reduction of wound size was achieved in 5 of 8 patients (62.5 %). The wound of one patient healed completely within the predetermined study time period. In the 22 patients with diabetic foot syndrome the healing rate of 19 patients could be analyzed. On the whole, 63.2 % of the patients had a wound size reduction of at least 50 % during treatment. Complete wound closure could be achieved in 21.1 % of the patients.

The stipulation that within the context of this study previously initiated concomitant, cause-oriented therapeutic measures, such as compression therapy in patients with venous leg ulcers or pressure relief in patients with pressure ulcers, be continued unaltered supports the conclusion that objective benefits can be attributed to the use of Tegaderm™ Matrix. As a control group is, however, lacking in the study design, the influence of further factors cannot be excluded. For patients in whom complete wound closure could not be achieved, further options of modern wound therapy are available [26, 27].

It should not be propagated on the basis of our results that Tegaderm™ Matrix is now the wound dressing that in the future should be used in all patients with chronic wounds. In every patient with a chronic wound, a treatment plan addressing underlying causes is mandatory. For example, it may include phlebologic surgery and compression therapy in patients with a venous leg ulcer. Nonetheless, when wound healing is stagnant despite therapy of the underlying factors in combination with modern moist wound therapy, it can in at least a proportion of the patients be activated by means of use of Tegaderm™ Matrix, for example. Nevertheless, suitable test systems that allow for a pre-selection of suitable patients are at present still lacking. Current announcements at scientific meetings suggest that such test systems allowing for individualized therapy will become available in the near future.

Conclusions

Tegaderm™ Matrix within the context of a cause-oriented therapy is a well-tolerated wound dressing that supports the activation of the wound healing process in over 70 % of patients with previously therapy-refractory chronic wounds. <<<

Conflicts of interest

The clinical study was commissioned by the 3M company (Neuss, Germany). Drs. Körber and Dissemond have in past years received honoraria for lectures for 3M. Dr. Dissemond has served as scientific consultant and overseen several clinical study projects for 3M.

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References

1 Dissemond J, Körber A, Grabbe S. Differentialdiagnosen des Ulcus cruris. J Dtsch Dermatol Ges 2006; 8: 627–34.
2 Körber A, Klode J, Al-Benna S, Wax C, Schadendorf D, Steinsträsser L, Dissemond J. Genese des chronischen Ulcus cruris bei 31 619 Patienten im Rahmen einer Expertenbefragung in Deutschland. J Dtsch Dermatol Ges 2011; 9: 116–22.
3 Dissemond J, Goos M, Wagner SN. Die Rolle von oxidativem Stress in der Pathogenese und Therapie chronischer Wunden. Hautarzt 2002; 53: 718–23.
4 Gill SE, Parks WC. Metalloproteinases and their inhibitors: regulators of wound healing. Int J Biochem Cell Biol 2008; 40: 1334–47.
5 Greener B, Hughes AA, Bannister NP, Douglass J. Proteases and pH in chronic wounds. J Wound Care 2005; 14: 59–61.
6 Schneider LA, Körber A, Grabbe S, Dissemond J. Influence of pH on wound-healing: a new perspective for wound-therapy? Arch Dermatol Res 2006; 298: 413–20.
7 Goldman RJ, Salcido R. More than one way to measure a wound: An overview of tools and techniques. Adv Skin Wound Care 2002; 15: 236–43.
8 Körber A, Weindorf M, Dissemond J. Exsudatmanagementkapazität moderner Wundauflagen für die Therapie des Ulcus cruris venosum unter Kompressionstherapie. Hautarzt 2008; 59: 904–11.
9 Körber A, Freise J, Rietkötter J, Grabbe S, Dissemond J. Erfolgreiche Behandlung therapierefraktärer chronischer Wunden mit DerMax. ZfW 2006; 11: 310–4.
10 Dissemond J, Witthoff M, Brauns TC, Haberer D, Goos M. Untersuchungen zum pH-Wert des Milieus chronischer Wunden im Rahmen einer modernen Wundtherapie. Hautarzt 2003; 54: 959–65.
11 van den Berg AJ, Halkes SB, van Ufford HC, Hoekstra MJ, Beukelman CJ. A novel formulation of metal ions and citric acid reduces reactive oxygen species in vitro. J Wound Care 2003; 12: 413–8.
12 Hampton S, Young S, Kerr A, King L. An observational study of the use of a polyhydrated ionogen impregnated dressing (DerMax) in the treatment of wounds. Poster shown at EWMA-Congress 2006, Prag.
13 Karim RB, Brito BL, Dutrieux RP, Lassance FP, Hage JJ. MMP-2 assessment as an indicator of wound healing: A feasibility study. Adv Skin Wound Care 2006; 19: 324–7.
14 Lassance FP, Karim RB, Brito B, Raaijmaker J, Joris Hage J. Analysis of morphological and immunhistological changes during treatment with DerMax. Wound Repair Regen 2003; 11: 53.
15 Pirayesh A, Dessy LA, Rogge FJ, Hoeksema HJ, Sinove YM, Dall' Antonia A, Jawad MA, Gilbert PM, Rubino C, Scuderi N, Blondeel R, Monstrey S. The efficacy of a polyhydrated ionogen impregnated dressing in the treatment of recalcitrant diabetic foot ulcers: a multi-centre pilot study. Acta Chir Belg 2007; 107: 675–81.
16 van Leen MWF, Lüning EWN, Neyens JCL, Schols JMGA. Naaldwijk. Analysis of morphological and immunohistochemical changes during treatment with Dermax®. WUWHS 2004, Paris.
17 Wang X, Li KF, Adams E, van Schepdael A. Matrix metalloproteinase inhibitors: a review on bioanalytical methods, pharmacokinetics and metabolism. Curr Drug Metab 2011; 12: 395–410.
18 Lobmann R, Ambrosch A, Schultz G, Waldmann K, Schiweck S, Lehnert H. Expression of matrix-metalloproteinases and their inhibitors in the wounds of diabetic and non-diabetic patients. Diabetologia 2002; 45: 1011–6.
19 Mwaura B, Mahendran B, Hynes N, Defreitas D, Avalos G, Adegbola T, Adham M, Connolly CE, Sultan S. The impact of differential expression of extracellular matrix metalloproteinase inducer, matrix metalloproteinase-2, tissue inhibitor of matrix metalloproteinase-2 and PDGF-AA on the chronicity of venous leg ulcers. Eur J Vasc Endovasc Surg 2006; 31: 306–10.
20 Xue M, Le NT, Jackson CJ. Targeting matrix metalloproteases to improve cutaneous wound healing. Expert Opin Ther Targets 2006; 10: 143–55.
21 Moor AN, Vachon DJ, Gould LJ. Proteolytic activity in wound fluids and tissues derived from chronic venous leg ulcers. Wound Repair Regen 2009; 17: 832–9.
22 Wiegand C, Schönfelder U, Abel M, Ruth P, Kaatz M, Hipler UC. Protease and pro-inflammatory cytokine concentrations are elevated in chronic compared to acute wounds and can be modulated by collagen type I in vitro. Arch Dermatol Res 2010; 302: 419–28.
23 Motzkau M, Tautenhahn J, Lehnert H, Lobmann R. Expression of matrix-metalloproteases in the fluid of chronic diabetic foot wounds treated with a protease absorbent dressing. Exp Clin Endocrinol Diabetes 2011; 119: 286–90.
24 van Rossum M, Vooijs DPP, Walboomers XF, Hoeckstra MJ, Spauwen PHM, Jansen JA. The influence of a PHI-5-loaded silicone membrane, on cutaneous wound healing in vivo. J Mater Sci Mater Med 2007; 18: 1449–56.
25 Gottrup F, Apelqvist J, Price P, EWMA Patient Outcome Group. Outcomes in controlled and comparative studies on non-healing wounds: Recommendations to improve the quality of evidence in wound management. J Wound Care 2010; 19: 237–68.
26 Dissemond J. Wundmanagement – State of the Art 2011. Kompendium Dermatologie 2011; 7: 26–9.
27 Dissemond J. Physikalische Therapien des chronischen Ulcus cruris. Hautarzt 2010; 61: 387–96.